ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2006, p. 1528–1530 Vol. 50, No. 4
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.4.1528–1530.2006

Microflora Changes with Norfloxacin and Pivmecillinam in Women with Recurrent Urinary Tract Infection

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Received 26 July 2005/Returned for modification 21 September 2005/Accepted 22 January 2006

Similar changes in the periurethral and vaginal microflora were observed in 19 women with recurrent urinary tract infection following treatment with norfloxacin (NOR) or pivmecillinam (PIV). *Escherichia coli* strains were suppressed by both treatments. *Staphylococcus* spp. and enterococci colony counts increased following PIV treatment in the periurethral flora but remained stable with NOR.

Uncomplicated lower urinary tract infection (UTI) in females is often successfully treated with antibiotics. However, many women experience relapses or reinfections. The pathogenesis of UTI involves, among other factors, colonization of the periurethral area and bladder by *Escherichia coli*, likely originating from the fecal microflora (6). Large numbers of enterobacteria were present on the introitus in women with recurrent UTI, compared to low numbers in women without UTI (1, 10, 12). Previous studies have shown that pivmecillinam (PIV) has minor effects on the normal oropharyngeal, intestinal, vaginal, and skin microflora (13, 14), and norfloxacin (NOR) strongly suppressed fecal enterobacteria in patients with UTI (2, 3) and showed a more pronounced effect on the vaginal flora compared to the fecal flora (11).

The objectives of this study were to compare the effects on the periurethral and vaginal microflora and time to normalization of NOR and PIV in females with recurrent lower UTI.

Twenty-five females, aged 18 to 55 years, with a history of recurrent lower UTI (≥2 UTI episodes, including the present one, during the last 6 months or ≥3 UTIs during the last 12 months) were enrolled in a randomized, double-blind study in 1993 to 1996. Inclusion criteria included a positive nitrite test and symptoms (urgency, frequency, dysuria, and/or suprapubic pain) of lower UTI and confirmed bacteriuria with *E. coli* or *Klebsiella pneumoniae.* Informed consent was obtained, and the Ethical Review Committee and Medical Product Agency approved the study protocol. Exclusion criteria included menopause or age above 55 years, known or clinically suspected pyelonephritis, and complicated UTI.

Seven days of treatment with either NOR, 400 mg twice a day (Lexinor; Astra), or PIV, 400 mg three times a day (Selexid; Leo Pharma), was randomly allocated in a double-blind fashion. Adverse events were spontaneously reported or observed.

Samples from the urine and periurethral and vaginal locations were obtained before start of treatment, visit 1 (day 1), and at two follow-ups, visits 2 and 3 (days 12 to 14 and 28 to 35, respectively). All samples were sent the same day and cultured at the Karolinska University Hospital Huddinge. The periurethral and vaginal sampling methods have been described previously (5, 7).

The complete gram-positive and gram-negative aerobic and anaerobic microflora were identified according to non-molecular-biological methods (4, 5, 8).

Significant bacteriuria, at the initial visit, was defined as $\geq 10^4$ CFU/ml of *E. coli* or *K. pneumoniae.* The bacteriological results were classified as follows: elimination, no bacteriuria ($\leq 10^3$ CFU/ml); persistence, continued growth of the initial pathogen ($\geq 10^4$ CFU/ml); relapse, return of the initial pathogen ($\geq 10^4$ CFU/ml); reinfection, growth of a new pathogen ($\geq 10^5$ CFU/ml) posttreatment.

Quantitative alterations in microbiological variables between visits were compared by using the Wilcoxon signed rank test for paired samples. P values of ≤ 0.05 were considered statistically significant.

Nineteen patients fulfilled the inclusion and exclusion criteria: 11 received NOR, and 8 received PIV. The patient characteristics did not differ between the two treatment groups. Six patients (two NOR and four PIV) were excluded (for UTI caused by *Staphylococcus saprophyticus*, beta-hemolytic streptococci, or *K. pneumoniae* [no follow-up data], nonrecurrent UTI, or above 55 years).

The observations from the aerobic periurethral flora following NOR treatment were that *Streptococcus* spp. were present in eight patients at visit 1 and remained in five patients at visit 3. *Enterococcus* spp. were isolated in seven patients initially, with six still colonized at visit 3. Likewise, nine patients had growth of *Staphylococcus* spp. at visit 1, and eight patients had these organisms at visit 3. However, of 11 patients with growth of *E. coli*, only 1 had growth (reduced counts) of *E. coli* at visits 2 and 3 ($P < 0.01$) and 1 patient reacquired *E. coli* at visit 3. Two of four patients remained colonized with *Candida* spp. from visit 1 to 3. One patient was recolonized, and one new patient acquired *Candida* spp. at visit 3.

For PIV treatment, *Streptococcus* spp. isolated in four patients initially remained in three and two patients at visits 2 and 3, respectively. One additional patient became colonized at

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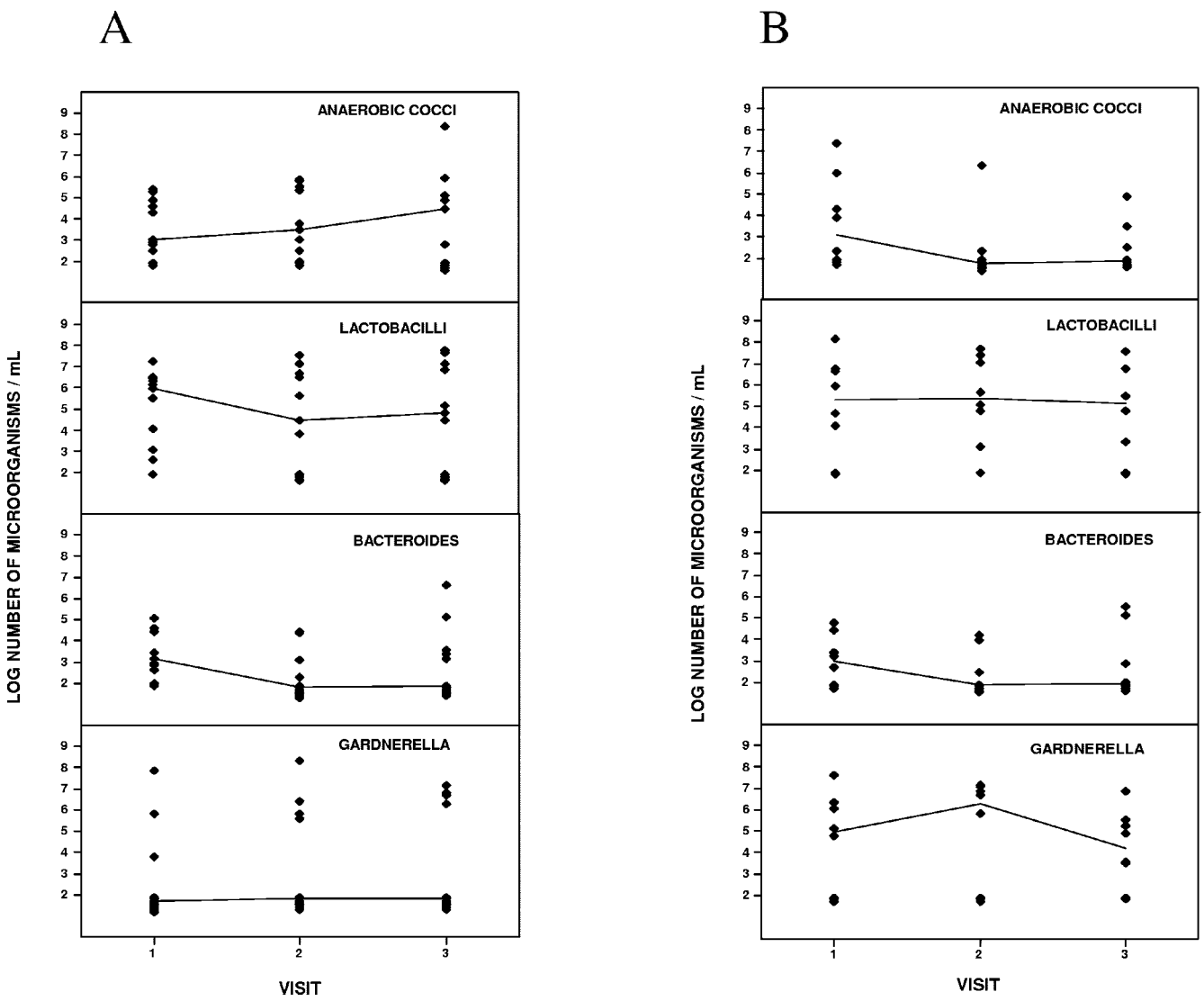

FIG. 1. Ecological impact of norfloxacin (A) and pivmecillinam (B) on the anaerobic periurethral flora. The straight lines show the median values.

visits 2 and 3. *Enterococcus* spp. present in three patients initially increased in colony count and appeared in three new patients at visit 2 and one additional patient at visit 3. *Staphylococcus* spp. increased from four patients being colonized initially to seven and five patients at visits 2 and 3, respectively. Six of eight patients had growth of *E. coli* initially, three remained colonized at visit 2 ($P < 0.05$), and three (one new patient) were colonized at visit 3. *Candida* spp. was present in one patient at visits 2 and 3. The colonization of the vagina was similar to the periurethral flora.

The impact of NOR and PIV on the anaerobic periurethral flora is shown in Fig. 1. Lactobacilli were isolated in 10 of 11 NOR patients initially, and 7 had growth of lactobacilli at visit 3. Six of eight PIV patients had lactobacilli initially, five remained colonized, and one new patient acquired lactobacilli at visits 2 and 3. The microflora of the vagina was similar to the periurethra.

Short-term bacteriological efficacy was achieved in 9 of 11 NOR patients and in 7 of 8 PIV patients, and accumulated (long-term) efficacy was seen in 8 of 11 and in 5 of 8 patients, respectively. Three patients had reinfections caused by *Enterococcus faecalis*, *Streptococcus* spp. group B, and lactobacilli; these bacteria were also present in the periurethral and vaginal flora.

In conclusion, antibiotic treatment of urinary tract infections should be effective and not cause major disturbances of the microflora (9, 15). In this study, the changes observed in the periurethral and vaginal flora with treatment of either NOR or PIV were similar.

Financial support was received from Glaxo Group Research Ltd., United Kingdom.

We thank Torsten Sandberg for advice.

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